

This article presents methods and results of surgery and radiotherapy of brain metastases from non-small cell lung cancer (BMF-NSCLC). Patients with single BMF-NSCLC, with Karnofsky score  $\geq 70$  and controlled extracranial disease are the best candidates for surgery. Stereotactic radiosurgery (SRS) is recommended in patients with 1–3 BMF-NSCLC below 3–3.5 cm, with minor neurological symptoms, located in parts of the brain not accessible to surgery, with controlled extracranial disease. Whole brain radiotherapy (WBRT) following SRS reduces the risk of local relapse; in selected patients median survival reaches more than 10 months. Whole brain radiotherapy alone is a treatment in patients with multiple metastases, poor performance status, uncontrolled extracranial disease, disqualified from surgery or SRS with median survival 3 to 6 months. There is no doubt that there are patients with BMF-NSCLC who should receive only the best supportive care. There is a debate in the literature on how to select these patients.

**Key words:** non-small cell lung cancer, brain metastases, radiation therapy.

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# Methods and results of locoregional treatment of brain metastases in patients with non-small cell lung cancer

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## Introduction

Lung cancer is the most common cause of brain metastases (40–50%), and comes before breast cancer (15–25%) and melanoma (5–15%) in this respect [1–6]. In patients with non-small cell lung cancer (NSCLC), accounting for 80–85% of all lung cancers, the risk of development of brain metastases (BMF-NSCLC) throughout the course of the disease is 30–50%; brain metastases are found in 7–10% of patients with NSCLC at diagnosis [7–18]. The risk of BMF-NSCLC development is significantly higher in patients with advanced NSCLC (stage III and IV) and in patients with adenocarcinoma and large-cell carcinoma, as compared to squamous-cell carcinoma histology [12–14, 19, 20]. Hsiao *et al.*, in an analysis of 482 patients with stage IIIB–IV NSCLC, found that the risk of brain metastasis was statistically significantly higher in women, patients aged less than 60 years and in patients with adenocarcinoma histology [7].

In over 50% of patients BMF-NSCLC occur synchronously, and in 45–50% of patients multiple focal lesions are found; 5–15% patients are asymptomatic and brain metastases are found in them on imaging studies [10, 12, 14].

Occurrence of BMF-NSCLC is associated with a very poor prognosis: median survival of untreated patients is about 1 month [1, 6, 8, 10, 11, 15, 17, 18, 21, 22] and of those receiving palliative corticosteroid treatment slightly over 2 months [17, 18]. Palliative whole brain radiotherapy (WBRT) prolongs median survival to 3–6 months [8, 10, 17]. For many years, these extremely poor treatment results caused exclusion of patients with BMF-NSCLC from any controlled clinical studies that investigated e.g. systemic treatment. However, in recent years a positive change has been observed [15, 22]. In patients qualified for definitive surgery or stereotactic radiosurgery (SRS), with or without WBRT, median survival reaches even more than 10 months; however, this is true only for selected patients: with good performance status, complete or very good extracranial disease control and 1–3 BMF-NSCLC [8, 15, 18, 23–27].

The following methods are used in the treatment of BMF-NSCLC: surgery, SRS, WBRT, systemic treatments (chemotherapy, immunotherapy) and various combinations of these methods [1, 2, 4–6, 8, 9, 11, 12, 17–19, 26, 28–35]. In general, local (surgery, SRS) [1, 4, 6, 8, 17, 18, 28–30, 35] or regional (WBRT) [1, 4, 19, 28–30, 33–35] treatment is preferred, including combination of sur-

ger and radiotherapy. There is a growing importance of systemic treatment, in particular of immunotherapy [1, 2, 4, 11, 12, 30–32].

## Surgery

Three controlled clinical studies have compared the efficacy of surgery combined with WBRT to that of WBRT alone, in patients with single brain metastasis, mainly from NSCLC [36–38]. The results of these studies are presented in Table 1.

In the study of Patchell *et al.*, median survival was 15 weeks in patients treated with radiotherapy alone and 40 weeks in the group of patients treated with surgery; time to relapse or progression of brain lesions was 21 weeks and 59 weeks, respectively [36]; both differences were highly statistically significant. The study by Vecht *et al.* has confirmed the statistically significant positive effect of surgery on patients' survival, expressed as prolongation of median survival by 12 months [37].

In a study by Mintz *et al.*, no improvement of survival of patients treated with surgery and WBRT was found, as compared to patients treated with WBRT alone. It should be stressed however that in this study, extracranial disease control was achieved in only 21% of patients, whereas in the previous two studies this control was found in over 60% of patients. Additionally, patients analysed by Patchell *et al.* had a MRI scan before surgery, whereas it was not done in any patient from the group studied by Mintz, which puts into question unifocality of brain lesions in the latter group [36, 38].

Qualification of patients for surgical treatment of BMF-NSCLC is based on assessment of three basic factors: patient's performance status, level of extracranial disease control and brain lesion status [4, 6, 30]. Patients with single BMF-NSCLC, with Karnofsky score (KPS) of 70 or more and controlled extracranial disease are the best candidates for surgery [4, 29]. According to Mamelak *et al.*, combination of surgery and WBRT in this group of patients allows 5-year survival to be achieved in 10–20% of patients [4].

It is however unquestionable that the level of extracranial disease control has a significant impact on the patient's future and on the decision whether to perform surgical treatment of BMF-NSCLC [23]. Analysis of the study of Mintz *et al.* clearly shows that the majority of deaths

resulted from locoregional NSCLC progression or from distant extracranial metastasis and not from the presence of BMF-NSCLC themselves [38]. In general, BMF-NSCLC surgery is not recommended for patients with life expectancy not exceeding 3 months [4, 6].

In some patients surgical treatment may be justified irrespective of the level of extracranial disease control; the following patients are included:

- patients with large (> 3 cm) tumours, causing significant neurological deficit and/or high intracranial hypertension (mass effect),
- patients with tumours located in the posterior cranial fossa, with a risk of secondary hydrocephalus or brain-stem compression,
- patients with haemorrhagic, necrotic or cystic tumours, with a surrounding oedema zone.

Nowadays, presence of more than one BMF-NSCLC is not a contraindication for surgical treatment of brain metastases; even if resection of all BMF-NSCLC is impossible, removal of one or more metastases that are particularly burdensome to the patient may be justified [6, 39–41]. Surgery may also be indicated in case of uncertain nature of brain lesions or if there is a need to determine biological features of BMF-NSCLC that may affect selection of e.g. targeted therapy [4, 6, 29].

Appropriate qualification of patients for surgical treatment of BMF-NSCLC ensures good tolerance and lack of complications. Improvement of local efficacy of BMF-NSCLC surgery may be expected along with progress of surgical technique, including in particular en bloc resections and resections with clear microscopic margins [29, 42, 43].

## Radiotherapy

### Stereotactic radiosurgery

Stereotactic radiosurgery may be performed with three types of radiation: high energy photons obtained from linear accelerators, gamma rays from a cobalt unit (gamma-knife) and relatively rarely, due to limited availability, with a proton beam from a cyclotron. According to protocol RTOG 90-05, the maximum tolerated single dose of radiation for a tumour of a diameter of 31–40 mm is 15 Gy, of 21–30 mm – 18 Gy and below 20 mm – 24 Gy [30, 35, 44]. Slightly lower doses are suggested for BMF-NSCLC located in or near the brain stem, optic nerves and optic chiasm [4].

**Table 1.** Results of controlled clinical studies comparing the efficacy of surgery combined with WBRT to that of WBRT alone

Authors, publication year, reference no.	% of patients with extracranial disease control	Method of treatment of brain metastases	Number of patients treated	Median survival	<i>p</i> log-rank test
Patchell <i>et al.</i> , 1990 [36]	62.5	WBRT surgery + WBRT	23 25	15 weeks 40 weeks	< 0.01
Vecht <i>et al.</i> , 1993 [37]	68.3	WBRT surgery + WBRT	31 32	3 months 15 months	0.04
Mintz <i>et al.</i> , 1996 [38]	21.4	WBRT surgery + WBRT	43 41	6.3 months 5.6 months	NS

NS – non-significant

Stereotactic radiosurgery is used as:

- the only treatment method for selected patients with BMF-NSCLC,
- the primary treatment method, followed by WBRT,
- a method of local dose escalation (boost) after WBRT,
- a method of treatment of BMF-NSCLC relapses, after both WBRT and SRS (re-SRS).

The best candidates for SRS treatment are patients:

- with single (1–3) BMF-NSCLC, of a diameter not exceeding 3–3.5 cm,
- with BMF-NSCLC located in all brain regions including those not accessible to surgery,
- with no or only minor neurological symptoms,
- with controlled extracranial disease [4, 30, 35].

Stereotactic radiosurgery efficacy in the treatment of BMF-NSCLC has been confirmed unequivocally in numerous retrospective and prospective studies [4, 8, 17, 18, 28, 30, 35, 44–59]. A response to SRS (decreased size of the metastasis or its growth inhibition) is found in 80–93% of patients, 1-year local control in 61–86% of patients; median survival ranges from 7 to 14 months [4, 8, 18, 35, 49, 50]. Acute toxicity develops in 5–18% of patients undergoing SRS, and includes headache, nausea, exacerbation of existing neurological symptoms, epilepsy; a late complication may be radiation-induced brain necrosis that is found in 2–6% of patients, with a clear association with SRS dose and with the size of the target volume [4, 35, 44].

In 2004, Hu *et al.* reported that in a group of patients with stage I NSCLC according to the AJCC, patients with single BMF-NSCLC had similar survival as patients with disease of the same stage without BMF-NSCLC, provided that an aggressive treatment (chemo-radiotherapy) of chest lesion and surgery or SRS of the brain metastasis were performed [56]. In 2008, Flannery *et al.* analysed a group of patients treated with curative intent for NSCLC, with a single synchronous BMF-NSCLC treated with SRS; median survival of patients was 18 months, and 5-year overall survival was 21% [57]. In 2010, Mariya *et al.* described a group of 84 patients treated initially with SRS; in 44 (52.4%) patients 1 metastasis was found, in 27 (32.1%) – 2, in 8 (9.5%) – 3, and in 5 (6.0%) more than 4 BMF-NSCLC. One- and 5-year overall survival was 38% and 11%, respectively, and median survival was 9 months. Fifteen patients survived over two years, of whom 97% (13/15) had 1 BMF-NSCLC at presentation, and brain metastases outside the irradiated (SRS) volume appeared only in 3/15 (20%) patients [8]. In 2011, Marko *et al.* presented an analysis of 26 patients with asymptomatic BMF-NSCLC, treated with SRS alone. In this group, KPS was 90–100, and the mean number of brain metastases was 1.6; 40 BMF-NSCLC were irradiated in total. Mean survival was 12.3 ± 4.3 months. The investigated group of patients was compared with groups of patients subject to WBRT alone (mean survival – 12.3 months), WBRT + SRS (mean survival – 12.7 months) and WBRT + surgery (mean survival – 20.2 months), matched with respect to clinical characteristics. The differences found were statistically insignificant [18].

There are numerous controversies in the literature about the role of WBRT as a treatment adjuvant to SRS [8, 35, 45–48, 54–56]. In retrospective studies Sneed *et al.* and

Hu *et al.* did not find any positive effect of adjuvant WBRT on survival [54–56]. In three controlled clinical studies, the efficiency of SRS versus SRS + WBRT was evaluated [45]. Studies by Aoyama *et al.* [47] and Kochera *et al.* [46] did not show any difference in patients' survival, but addition of WBRT statistically significantly improved local and distant (brain areas outside the SRS volume) control. The effectiveness of WBRT combined with an SRS boost used in the treatment of 1–3 brain metastases was compared with that of WBRT alone [35, 45, 51–53]. In a study of Andrews *et al.* (RTOG 9508), in a group of patients with single, inoperable brain metastasis, statistically significant improvement of median survival was achieved, from 4.9 to 6.9 months, after combined treatment with WBRT + SRS. In patients with 2 or 3 metastases, only improvement of local control was observed. Local control improvement, without overall survival improvement after WBRT + SRS treatment, was also found by Sanghavi *et al.* [50], Stafiński *et al.* [52] and Patil *et al.* in a meta-analysis presented in 2013 [53].

Many authors have reported the feasibility and efficacy of repeated SRS, as a salvage therapy, in the treatment of local recurrences of BMF-NSCLC after previous irradiation, in a highly selected group of patients [17, 35, 44, 58, 60, 61].

To conclude, SRS alone may be used in selected patients with single BMF-NSCLC, without neurological symptoms, having a good performance status (KPS – 90–100), with controlled extracranial disease. These patients need regular follow-up with frequent visits, as according to the literature 20–50% of them develop new BMF-NSCLC in regions outside the SRS volume, and they sometimes experience local recurrences that are amenable to further treatment (e.g. repeated radiotherapy or surgery) [8, 28, 30, 62]. Literature data show clearly that WBRT following SRS reduces the risk both of local relapse and of development of metastases in parts of the brain outside the SRS volume. In patients with single metastasis, addition of SRS to initial WBRT improves patients' survival, and in patients with multiple metastases it improves local control without any effect on survival.

### Whole brain radiotherapy

For several decades, WBRT combined with corticosteroid treatment has been a basic method of treatment of patients with BM-NSCLC. Whole brain radiotherapy alone is indicated primarily in patients:

- with multiple BM-NSCLC,
- not qualifying for surgery or SRS,
- with poor performance status,
- with uncontrolled extracranial disease.

Whole brain radiotherapy is also used as an adjuvant to surgery, and similarly as in the case of combination with SRS it allows for reduction of the number of brain metastasis relapses [1, 4, 15, 19, 29, 30, 35–37].

Radiotherapy doses used in WBRT range from 20 to 40 Gy, given in 5–20 fractions; the most common is the regimen administering 30 Gy in 10 fractions, and the majority of authors avoid administration of fraction doses higher than 3 Gy [30, 33, 35]. Levy *et al.* suggest a possibility of improvement of WBRT efficacy, in patients with

single BMF-NSCLC, disqualified from surgery or SRS, by escalation of the dose to the metastatic lesion with photons from a linear accelerator [34].

Whole brain radiotherapy has a modest effect on survival of patients with BMF-NSCLC; median survival after this treatment ranges from 3 to 6 months [4, 5, 19, 28, 30, 63], and half of patients die due to progression of brain metastases [30]. 47–56% of patients respond to the treatment [4, 30, 35]. However, WBRT allows for: reduction of the dose of corticosteroids, improvement of neurological symptoms, improvement of quality of life, and survival prolongation in comparison to corticosteroid treatment alone [4, 19].

#### Whole brain radiotherapy vs. best supportive care

There is no doubt that there is a group of patients with BMF-NSCLC who do not benefit from WBRT and should receive only best supportive care (BSC); however, precise selection of these patients remains difficult [5, 64–66]. In a prospective study by Bezjak *et al.*, 55% of patients with brain metastases had obvious progression or died during the first month after WBRT [64].

In a retrospective study conducted by Sundaresan *et al.* (2010), 23% of analysed patients with brain metastases from lung cancer died during the first 6 weeks [65]; the authors tried to develop a prognostic index for these patients with multiple brain metastases that would allow for selection of patients who would not benefit from WBRT because of a too short life expectancy. ECOG (Eastern Cooperative Oncology Group) performance status was the sole statistically significant prognostic factor.

In 2012, Craighead and Chan defined benefit from WBRT as survival of over 3 months after diagnosis of brain metastases [63]. The results of their study suggest that patients from category 2 and 3 according to RPA-RTOG (recursive partitioning analysis – Radiation Therapy Oncology Group) [67], with more than 3 metastases, do not benefit from WBRT, due to a short life expectancy (median survival 3.9 and 2.8 months, respectively) [63]. RPA-RTOG criteria

are presented in Table 2, and RECIST 1.1 (Response Evaluation Criteria in Solid Tumours) response criteria for primary and metastases of the brain are presented in Table 3.

In 2013, Windsor *et al.* presented a group of 3459 patients subject to WBRT due to brain metastases from various cancers [5]. After WBRT, 312 (17%) out of 1800 patients with lung cancer survived 6 months or less, and 1498 (83%) survived more than 6 months. The results showed that older patients (median age – 64 vs. 61 years) and patients with a shorter interval between lung cancer diagnosis and WBRT (31 vs. 35 weeks) had worse survival; these differences were statistically significant. Concluding their study, definition of the group of patients for whom BSC is a better solution remains a challenge for investigators. In 2013, preliminary results of a controlled clinical study of the Medical Research Council, QUARTZ, were published. The study compared the results of WBRT with BSC in patients with BMF-NSCLC; 85% of patients in the WBRT group and 99% in the BSC group were in category 2 and 3 according to RPA-RTOG criteria. Preliminary results of this study showed that using BSC alone did not worsen patients' survival or their quality of life (median survival 1.6 vs. 1.7 months) [68]. In the same year (2013) a study by Nieder *et al.* was published, which was similar to the QUARTZ study. In 41 patients BSC alone was used, in 41 WBRT with a dose of 30 Gy/10 fr., and in 31 WBRT with a dose of 20 Gy/5 fr.; median survival of all patients was 2.0 months, and in the groups listed above it was 1.7, 2.2 and 2.2 months respectively; the authors confirm in general the conclusions of the QUARTZ study [33].

#### Whole brain radiotherapy complications

Tolerance of WBRT is usually good, and early reactions are usually mild and resolve within several weeks after irradiation; they include mainly headache, fatigue, nausea and hair loss. Other early complications ( $\leq 6$  months), in the form of a syndrome including somnolence, short-lasting memory disturbances and mild leukoencephalopathy, are also transient in nature. However, a serious problem

**Table 2.** RPA-RTOG criteria

Prognostic factors	Class I	Class II	Class III
Age (< 65 vs. > 65 years)	All good prognostic factors	Other patients	KPS < 70
Performance status (KPS < 70 vs. $\geq 70$ )			
Extracranial metastases (yes vs. no)			
Controlled primary (yes vs. no)			

**Table 3.** RECIST 1.1 (Response Evaluation Criteria in Solid Tumours) – response criteria for primary and metastases of brain

RECIST 1.1. Response criteria for target lesions	
Complete response (CR)	Disappearance of all target lesions
Partial response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study and at least 5 mm increase or the appearance of one or more new lesions
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

is late complications (> 6 months after radiotherapy) that are in general irreversible, usually progressive and even life-threatening. The risk of developing the most serious of them, i.e. radiation-induced necrosis, is lower than 1% with appropriately dosed WBRT; encephalopathy occurs in 2–18% of patients, usually after 2 years following radiotherapy. Demyelination lesions and vascular damage may lead to memory, concentration and attention disturbances, mood swings, neurocognitive function (NCF) disorders and even dementia [19, 29, 35, 69]. It should be however kept in mind that many of these complications may be related to causes other than WBRT, e.g. disease progression, previous treatment (surgery, systemic treatment), anticonvulsants, patient's age, concomitant diseases (atherosclerosis, diabetes), etc. [19, 29, 35]. Prevention of late WBRT complications includes mainly: avoidance of exceeding fraction doses of 3 Gy, hippocampal sparing radiotherapy, and use of neuroprotective agents (memantine, donepezil, lithium, renin-angiotensin system blockers, etc.) [19].

To conclude, WBRT, due to its efficacy and lack of good alternative treatment options, remains a basic treatment for patients with multiple BMF-NSCLC and poor performance status.

## Summary

In summary, surgical treatment is recommended in patients with single BMF-NSCLC, with good performance status (KPS of 70 or more) and controlled extracranial disease. Patients with single (1–3) BMF-NSCLC of diameter below 33.5 cm, with no or only minor neurological symptoms, located in different regions of the brain, including those not accessible to metastasectomy, with controlled extracranial disease, are the best candidates for SRS. Whole brain radiotherapy following SRS reduces the risk of local relapse and progression of brain metastases outside the SRS volume. Whole brain radiotherapy alone, due to its efficacy and lack of good alternative treatment options, remains a basic treatment for patients with multiple BMF-NSCLC, poor performance status, with uncontrolled extracranial disease, disqualified from surgery or SRS.

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